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Copper-Catalyzed Oxidative Multicomponent Annulation Reaction for Direct Synthesis of Quinazolinones via an Imine-Protection Strategy

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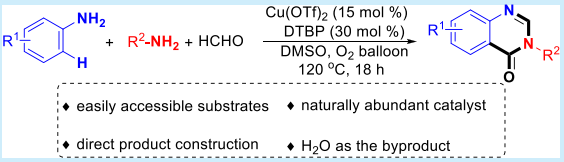
Supporting Information

ABSTRACT: Via an imine-protection strategy, we herein present an unprecedented copper-catalyzed oxidative multicomponent annulation reaction for direct synthesis of quinazolinones. The construction of various products is achieved via formation of three C−N and one C−C bonds in conjunction with the benzylic functionalization. The merits of easily available feedstocks, naturally abundant catalyst, good functional group and substrate compatibility, and release of H_2O as the byproduct make the developed chemistry a practical way to access quinazolinones.

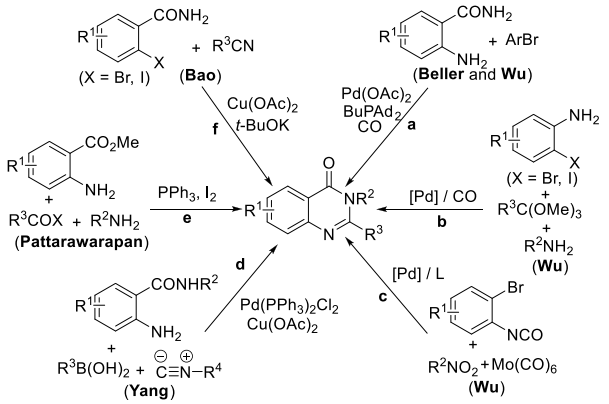


Quinazolinones constitute an important class of N-heterocycles. To date, numerous relevant compounds have been found to exhibit diverse biological and therapeutic activities, such as antitubercular, antiproliferation, antivirus, anticancer, antihypertension, antidepressant, antifungal, and antiulcer.[1] In addition, quinazolinones have been utilized as useful building blocks[2] for various synthetic purposes and the development of functional materials.[3] Consequently, the search for efficient methods to access quinazolinones is of high importance in the scientific community. Generally, the goal is realized by the oxidative condensation of 2-aminobenzamides with aldehydes or the equivalents.[4] In addition, other representative approaches are listed in Scheme 1: (1) via the strategy of palladium-catalyzed carbonylation followed by cyclization, the Beller and Wu groups have developed several protocols by employing the combinations of anthranilamides with aryl bromide (method **a**),[5a] 2-haloanilines with trimethoxymethanes and amines (method **b**),[5b,c] and 1-bromo-2-isocyanatobenzenes with nitro compounds (method **c**),[5d] respectively; (2) palladium-catalyzed three-component coupling of anthranilamides with isocyanides and arylboronic acids (method **d**);[6] (3) Ph_3P-I_2-mediated cyclization of anthranilic esters with N-substituted amides (method **e**);[7] (4) and the Cu-catalyzed addition of 2-halobenzamide to nitriles followed by SNAr reaction (method **f**).[8] More recently, our group has demonstrated a synthesis of ring-fused quinazolinones via direct oxidative functionalization of cyclic amines with 2-aminoarylmethanols.[9]

Despite the significant utility, all of the above transformations are based on the utilization of 1,2-difunctional benzenes, such as anthranilamides, 2-haloanilines, anthranilic esters, 2-haloisocyanatobenzenes, and 2-aminoarylmethanols. The key issue is that the preparation of these reactants generally requires multiple prefunctionalization steps.[10] As a result, the application of these protocols toward synthetic diversity is easily restricted. From the viewpoint of step and atom-economic concerns, the development of shortcuts enabling direct access to quinazolinones from readily available feedstocks, preferably monofunctional benzenes, would be highly desirable. However, to the best of our knowledge, it has remained an unresolved goal.

As our sustained effort toward the construction of functional N-heterocycles,[11] we have recently reported an aerobic copper-catalyzed synthesis of benzimidazoles from diarylamines and

Scheme 1. Existed Syntheses of Quinazolinones



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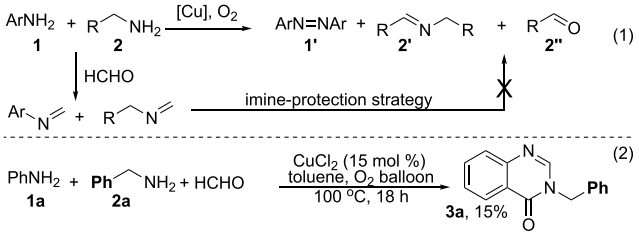
alkylamines via tandem triple C−H aminations, and benzimidazolones from diarylamines and dialkylamines via tandem C−H aminations[11a] and alkyl deconstructive carbofunctionalization.[11b] However, the utilization of the most easily available primary anilines **1** and alkylamines **2** in both cases generated the azo compounds **1′** via dehydrogenative dimerization of **1**,[12] and imines **2′** and aldehydes **2′′** via dehydrogenation and hydrolysis of the alkylamines **2** (Scheme 2, eq 1).[13] To avoid the formation

Scheme 2. Newly Observed Synthetic Protocol

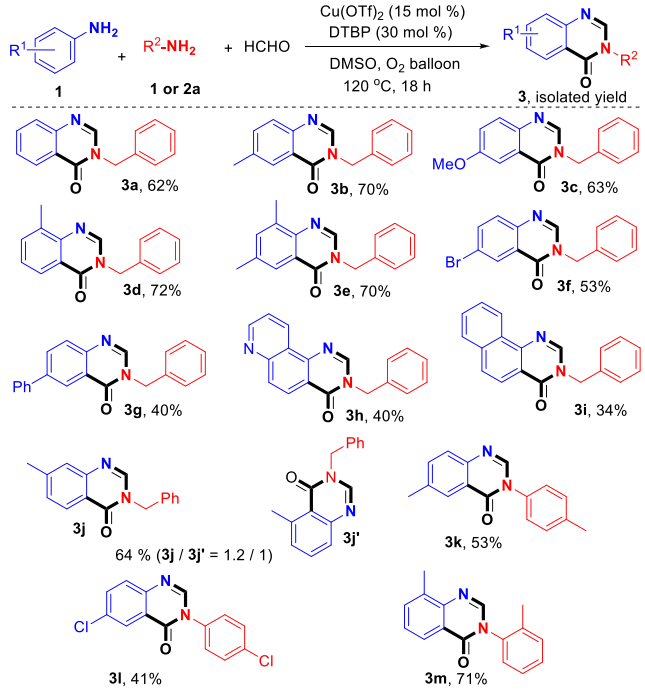


of these undesired products, we envisaged that an imine-protection strategy with formaldehyde might offer a solution (Scheme 2, eq 1), as the presence of formaldehyde in the aerobic copper-catalyzed reaction of **1** and **2** initially forms the imine intermediates via a condensation step, and the single-electron oxidation (SEO) of the electron-rich amines **1** and **2** is therefore suppressed.[11] Interestingly, when we performed the reaction of aniline **1a**, benzylamine **2a**, and formaldehyde in toluene at 100 °C for 18 h with a $CuCl_2/O_2$ system, we observed that, instead of anticipated benzimidazoles[11a] or benzimidazolones,[11b] a quinazolinone **3a** was detected in 15% yield (Scheme 2, eq 2). Based on this finding, we wish herein to report, for the first time, a copper catalyzed oxidative three-component annulation reaction for direct synthesis of quinazolinones from easily available anilines, alkylamines, and HCHO.

To formulate a more efficient reaction system, we chose the synthesis of product **3a** from aniline **1a**, benzylamine **2a**, and HCHO as a model system to evaluate different reaction parameters (Table S1 in the SI). Initially, we tested several HCHO equivalents by performing the reaction at 100 °C for 18 h, including paraformaldehyde, methanol, DMSO, and DMF.[14] However, all of them failed to give the desired product **3a** (entries 1−4, Table S1). Then, the screening of various copper catalysts and solvents showed that the combination of $Cu(OTf)_2$ and DMSO exhibited the best performance (Table 1, entries 5−10). By using $Cu(OTf)_2$ and DMSO as the preferred catalyst and solvent, respectively, the increase of reaction temperature to 120 °C is sufficient to improve the yield to 58% (entries 11 and 12). Further, the presence of acid additives has little influence on the product yields (entry 13), whereas the bases significantly diminished the yields (entry 14). Interestingly, additional oxidant evaluation (entries 15−17) led us to find that the introduction of 30 mol % of di-*tert*-butyl peroxide (DTBP) could further improve the yield to 72%. However, the use of excess DTBP under O_2-free conditions failed to generate product **3a** (entry 18). Thus, the optimal conditions are as shown in entry 15 of Table S1 (standard conditions).

With the optimal reactions in hand, we then examined the generality and the limitation of the synthetic protocol. Benzylamine **2a** was further employed to couple with various anilines (**1a**−**1i**, **1k** for their structures, see Scheme S1 in SI) and HCHO. As shown in Scheme 3, all the reactions proceeded

Scheme 3. Variation of Arylamine



smoothly and furnished the desired 3-*N*-benzyl-4(3*H*)-quinazolinones in reasonable to good yields upon isolation (Scheme 3, **3a**−**3i**). Various functional groups on the aryl ring of anilines **1** are well tolerated, and their electronic properties significantly influenced the product formation. Especially, anilines **1** containing electron-rich groups afforded the products (**3b**−**3e**) in higher yields than those having an electron-withdrawing group (**3f**−**3g**), presumably because the electron-rich anilines enhance the nucleophilicity of the reaction intermediates, thus favoring the cyclization process. Such a hypothesis is further supported by the fact that anilines containing a strong electron-withdrawing group (i.e., $-CF_3$, $-CO_2Et$, and $-NO_2$) were unable to afford the desired products. Gratifyingly, ring-fused arylamines, such as 5-aminoquinoline **1h** and 1-naphthylamine **1i**, could be transformed into the extended π-conjugated products **3h** and **3i** in acceptable yields. As expected, two regioisomers (**3j**, **3j′**) in a combined yield of 64% were detected when meta-substituted aniline **1k** was employed as a substrate, and compound **3j** from the cyclization occurring at the sterically less-hindered site constitutes the major product. The reactions of two anilines (**1b**, **1d**, and **1j**) with HCHO also underwent efficient cyclization, affording the 3-*N*-aryl quinazolinones in moderate to good yields (**3k**−**3m**). Noteworthy, a small amount of 3-*N*-aryl quinazolinones were also detected when the reactions employed anilines and alkylamines as the coupling partners; the highly selective generation of 3-*N*-alkyl quinazolinones (**3a**−**3j**) is assigned to the better reactivity of alkylamines than the anilines.

Subsequently, we turned our attention to the variation of primary alkylamines **2**. As illustrated in Scheme 4, all the reactions underwent smooth dehydrogenative cyclization, affording the 3-alkyl-4(3*H*)-quinazolinones in moderate to good isolated yields. Similar to the results described in Scheme 3, various functional groups (−Me, −OMe, −Br, and −Cl) on amines (**2b**−**2h**, **2n**−**2o**) were compatible with the transformation (**3m**−**3s**, **3z**−**3aa**). Benzylamines **2** containing an

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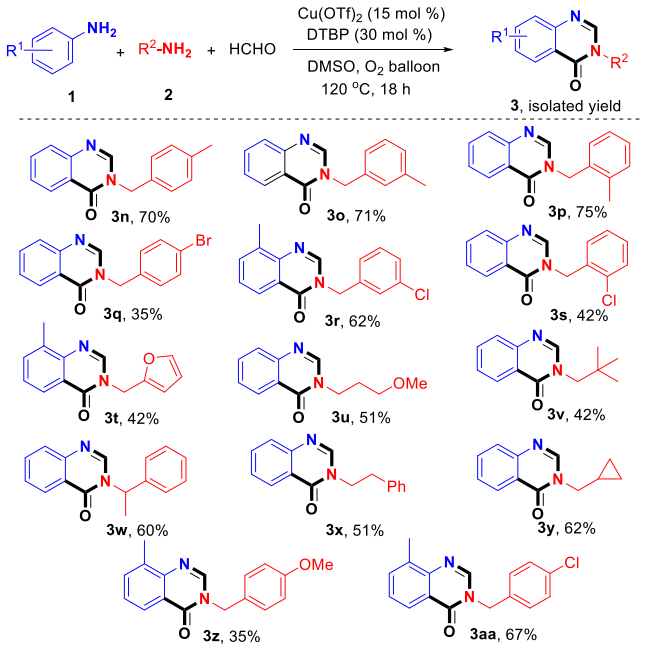
Scheme 4. Variation of Alkylamines



electron-donating group afforded the corresponding products in relatively higher yields (**3m**–**3o**) than those bearing an electron-withdrawing group (**3p**–**3r**). However, due to the relatively easier decomposition of the 4-bromobenzyl amine (**2e**) and 4-methoxybenzylamine (**2n**), they generated the corresponding products (**3q** and **3z**) in lower yields than the products (**3s** and **3aa**) arising from 2- and 4-chlorobenzylamines (**2g** and **2o**). Further, primary aliphatic amines, such as 3-methoxypropylamine (**2i**), neopentylamine (**2j**), *α*-methylbenzylamine (**2k**), phenethylamine (**2l**), and aminomethylcyclopropane (**2m**), were effectively transformed in combination with aniline **1a** and HCHO into the 3-*N*-alkyl-4(3*H*)-quinazolinones in moderate yields (**3u**–**3y**).

To gain mechanistic insights into the reaction, a time–yield profile of the coupling of *o*-toluidine **1d** and HCHO utilizing the optimal conditions was depicted in Figure 1. The substrates were rapidly consumed to form imine **1d′** within 15 min. Meanwhile, dihydroquinazoline **3m′** was accumulated to a maximum yield in 0.5 h and then gradually converted into quinazolinone **3m** in 6 h. The results indicate that both **1d′** and **3m′** are the key reaction intermediates. A similar time–yield profile was observed by monitoring the coupling of *o*-toluidine **1d**, benzylamine **2a**, and HCHO (see SI, Figure S1b).

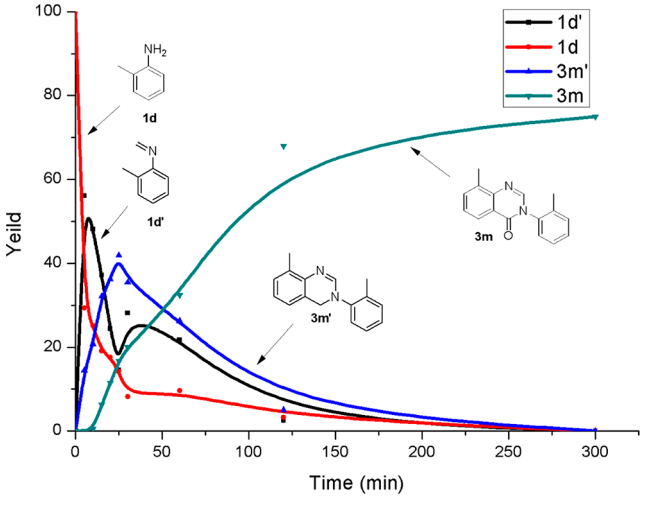
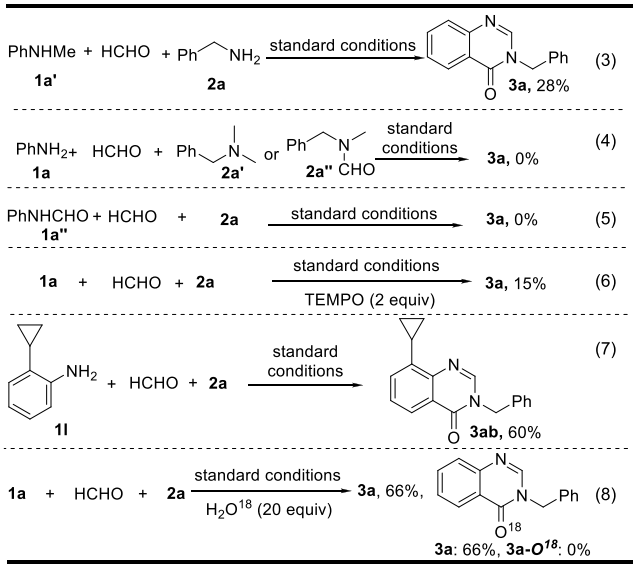


Figure 1. Representative time course of the reaction.

In consideration that a small portion of *N*-methylated products (**1a′** and **2a′**, Scheme 5) and the formamides (**1a′′** and **2a′′**, Scheme 5) were observed in the model reaction, we therefore tested the reactions of these four compounds with the other two coupling partners, respectively (Scheme 5, eqs 3–5). The results showed that, except for *N*-methylaniline **1a′**, compounds **1a′′**, **2a′**, and **2a′′** failed to give product **3a**. The phenomenon is rationalized as the oxidation of **1a′** can easily form the imine,[13] a key reaction intermediate proposed in Scheme 2. Further, the addition of excess TEMPO in the model reaction significantly suppressed the product formation (eq 6), implying that the reaction involves a radical process. 2-Cyclopropylaniline **1l** as a radical probe was utilized to react with HCHO and amine **2a**, which produced compound **3ab** in 60% yield with retention of the cyclopropyl unit (eq 7). The results indicate that, due to the formation of imine intermediates, the presence of HCHO prevents the single-electron oxidation of amines **1m** and **2a**. Thus, the radicals should generate after the cyclization process. Finally, the addition of excess H_2O^{18} in the model reaction did not produce even a trace of O^{18}-labeling product (**3a**-O^{18}), suggesting that the benzylic O atom arises from the oxidants, instead of H_2O (eq 8).

Scheme 5. Control Experiments



Based on the above findings, two plausible reaction pathways are depicted in Scheme 6. In path **a**, the presence of HCHO condenses with both amines **1** and **2** to form imines **1′** and **2′**. Then, the [4 + 2] cycloaddition[15] between **1′** and **2′** followed by isomerization would result in aminal **C**. Alternatively, the addition of alkylamine **2** to imine **1′** followed by a condensation of aminal **A** with HCHO would yield iminium **B**, and the subsequent intramolecular Friedel–Crafts-type[11c,d] aminoalkylation at the *ortho*-site of the aryl ring in **B** also rationalizes the formation of aminal **C**. Further, the single-electron oxidation-induced dehydrogenation[11a,b,16] of **C** under oxidative copper catalysis generates the dihydroquinazoline **D**. Finally, the

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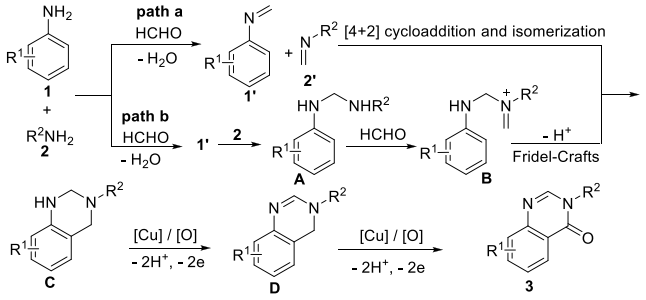
Scheme 6. Plausible Reaction Pathways



copper-catalyzed benzylic oxidation[17] gives rise to the desired product **3**. Noteworthy, in consideration that the electron-rich anilines are beneficial to the product formation (see Schemes 3 and 4), path b is believed to be a favorable pathway.

In summary, through an imine-protection strategy, we have developed an unprecedented aerobic copper-catalyzed three-component annulation reaction for direct synthesis of quinazolinones. Being different from the existed approaches utilizing bifunctional benzenes, the present protocol furnishes the products from readily available anilines, primary amines, and HCHO via the formation of three C−N and one C−C bonds in conjunction with the benzylic functionalization. The significant merits of good functional group and substrate compatibility, release of H_2O as the byproduct, and the use of the naturally abundant catalyst makes the developed chemistry a valuable approach in the construction of quinazolinones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01608.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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